Application No.: 10/799,386 Docket No.: 391442005902

AMENDMENTS TO THE SPECIFICATION

[0001] This application is a divisional ~~continuation~~ of U.S. patent application serial number 10/031,812, now U.S. patent 6,734,191 ~~allowed~~, which claims priority under 35 U.S.C. 119(e) from Provisional Applications 60/232,891 filed 15 September 2000; 60/234,510 filed 22 September 2000; Application 60/233,087 filed 15 September 2000; and Application 60/234,816 filed 22 September 2000. The contents of these applications are incorporated herein by reference.

On pages 36-38 of the specification, please make the following amendments to the specification:

[0111] Using the procedure of P. Wipf et al. (A.J. Phillips, Y. Uto, P. Wipf, M. J. Reno and D. R. Williams *Org. Lett.* **2000**, *2(8)*, 1165-1168), a –20 °C solution of N-(t-butoxycarbonyl)-Gly-Ser-OMe (170 mg, 0.615 mmol) in dichloromethane (5 mL) was treated with bis(2-methoxyethyl)aminosulfur trifluoride (0.125 mL, 0.677 mmol). The resulting solution was then stirred at –20 °C for 30 minutes, and bromotrichloromethane (0.212 mL, 2.21 mmol) was added, followed by DBU (0.330 mL, 2.21 mmol). The reaction was allowed to warm to 0 °C, and was stirred at that temperature for 5 hours, then aqueous ammonium chloride (5 mL) was added. After separation of the aqueous and organic layers, the aqueous layer was extracted twice with dichloromethane. The combined organic fractions were then dried over anhydrous sodium sulfate and concentrated. Purification by chromatography on silica gel (2% methanol in dichloromethane), gave ~~methyl 1-[*N*-(*t*-butoxycarbonyl)-aminomethyl]-oxazole-3-carboxylate~~ 2-(tert-butoxycarbonylamino-methyl)-oxazole-4-carboxylic acid methyl ester as an oil (123 mg, 78%). ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 3.88 (s, 3H), 4.51 (d, 2H, J = 5.8 Hz), 5.22 (br s, 1H), 8.19 (s, 1H)

[0112] The ester (178 mg, 0.695 mmol) in 0 °C dichloromethane (8 mL) was treated with DIBAL-H (1 M in dichloromethane, 2.08 mL, 2.08 mmol). The mixture was then stirred at 0 °C for 2 hours before being treated with aqueous 5% sodium potassium tartrate (8 mL). The mixture was stirred rapidly for 30 minutes (until the aqueous and organic layers clarified), and the layers were then separated. The aqueous layer was extracted twice with dichloromethane. The combined organic fractions were then dried over anhydrous sodium sulfate and concentrated.

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Purification by chromatography on silica gel (5% methanol in dichloromethane) gave ~~1-[*N*-(*t*-butoxycarbonyl)-aminomethyl]-3-hydroxymethyloxazole~~ (4-hydroxymethyl-oxazol-2-ylmethyl)-carbamic acid tert-butyl ester as an oil (45 mg, 28%). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 4.43 (d, 2H, J = 5.6 Hz), 4.56 (s, 2H), 5.37 (s, 1H), 7.54 (s, 1H).

[0113] To a stirred solution of ~~1-[*N*-(*t*-butoxycarbonyl)-aminomethyl]-3-hydroxymethyloxazole~~ (4-hydroxymethyl-oxazol-2-ylmethyl)-carbamic acid tert-butyl ester (45 mg, 0.197 mmol) in dichloromethane (5 mL) was added triethylamine (0.055 mL, 0.4 mmol) followed by methanesulfonyl chloride (0.023 mL, 0.3 mmol). The resultant solution was stirred at room temperature for 20 minutes, before being treated with an aqueous saturated ammonium chloride solution (5 mL). The aqueous layer was extracted twice with dichloromethane. The combined organic fractions were then dried over anhydrous sodium sulfate and concentrated to afford the desired mesylate, which was used directly and immediately in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.07 (s, 3H), 4.43 (d, 2H, J = 5.6 Hz), 5.15 (s, 2H), 7.73 (s, 1H).

[0114] Using General Procedure for N-Alkylation, ~~*O*-methanesulfonyl-1-[*N*-(*t*-butoxycarbonyl)-aminomethyl]-3-hydroxymethyloxazole~~ methanesulfonic acid 2-(tert-butoxycarbonylamino-methyl)-oxazol-4-ylmethyl ester (0.197 mmol) was stirred in 60°C acetonitrile (5 mL) for 4 hours with diisopropylethylamine (0.05 mL, 0.295 mmol) and (1*H*-*N*-*t*-butoxycarbonyl-benzimidazol-2-ylmethyl)-(5,6,7,8-tetrahydroquinolin-8-yl)-amine (95 mg, 0.25 mmol). The reaction was then cooled and concentrated. The residue was taken up in dichloromethane and extracted with aqueous ammonium chloride, dried, concentrated and purified by chromatography on silica gel (20:1 dichloromethane:methanol) to afford ~~[*N*-(*t*-(butoxycarbonyl)benzimidazol-2-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-yl)-{[1-N-(t-butoxycarbonyl)-aminomethyl]-benzoxazol-3-ylmethyl}-amine~~ 2-{[[2-(tert-Butoxycarbonylamino-methyl)-oxazol-4-ylmethyl]-(5,6,7,8-tetrahydro-quinolin-8-yl)-amino]-methyl}-benzoimidazole-1-carboxylic acid tert-butyl ester (23 mg, 19%). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.63 (s, 9H), 1.91 (m, 1H), 2.02 (m, 1H), 2.24 (dq, 1H, *J* = 6.8, 2.1 Hz), 2.51 (m, 1H), 2.61-2.78 (m, 2H), 4.27 (m, 1H), 4.43 (d, 2H, *J* = 5.8 Hz), 4.49 (s, 2H), 4.73 (d, 1H, *J* = 16.1 Hz), 5.09 (d, 1H, *J* = 16.1 Hz),

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5.15 (m, 1H), 6.88 (dd, 1H, J = 7.1, 5.4 Hz), 7.13 (d, 1H, J = 7.1 Hz), 7.24 (m, 2H), 7.61 (s, 1H), 7.61 (m, 1H), 7.74 (m, 1H), 8.23 (d, 1H, J = 5.4 Hz).

[0115] ~~[*N* (*t* (butoxycarbonyl)benzimidazol 2 ylmethyl] 5,6,7,8 tetrahydroquinolin 8 yl) {[1 N (t butoxycarbonyl) aminomethyl] benzoxazol 3 ylmethyl} amine~~ 2-{[[2-(tert-Butoxycarbonylamino-methyl)-oxazol-4-ylmethyl]-(5,6,7,8-tetrahydro-quinolin-8-yl)-amino]-methyl}-benzoimidazole-1-carboxylic acid tert-butyl ester (23 mg 0.039 mmol), was taken up in acetic acid (1 mL), to which a saturated solution of HBr in acetic acid (1 mL) was added. The mixture was then stirred, precipitated and isolated as per procedure D to yield **AMD9903** as a white crystalline solid (14mg). ^{1}H NMR (D_2O). δ 1.84 (m, 1H), 2.05 (m, 2H), 2.21 (m, 1H), 3.00 (m, 2H), 3.72 (d, 1H, J = 14.1 Hz), 3.92 (d, 1H, J = 14.1 Hz), 3.99 (d, 2H, J = 6.0 Hz), 4.39 (d, 1H, J = 16.5 Hz), 4.58 (d, 1H, J = 16.5 Hz), 4.72 (m, 1H), 7.59 (m, 2H), 7.75 (m, 2H), 7.84 (s, 1H), 7.86 (m, 1H), 8.33 (d, 1H, J = 8.1 Hz), 8.67 (d, 1H, J = 5.8 Hz). ^{13}C NMR (D_2O) δ 20.35, 20.57, 27.62, 35.70, 46.40, 48.16, 60.94, 114.15 (2C), 125.95, 127.06 (2C), 139.57, 140.46, 148.03, 151.23, 154.96. ES-MS *m/z* 389 (M+H); Anal. Calcd. for ($C_{22}H_{24}N_6O$ x 4 HBr x 2.6 H_2O): C, 34.82; H, 4.41; N, 11.07; Br 42.11. Found: C, 35.10; H, 4.44; N, 10.73; Br, 41.80.

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